REMARKS

Claims 29-31 are pending in the above-referenced application. Claims 1-28 and 32-35 have been withdrawn as being directed to a non-elected invention. As will be discussed in further detail below, claims 29-31 have been amended to more distinctly claim that which Applicants regard as their invention. The amendments to claims 29-31 should not be construed as acquiescence to the Examiner's position. Applicants do reserve the right to pursue in subsequently filed continuation and/or divisional application cancelled subject matter.

Furthermore, new claims 36-41 have been added to recite specific embodiments. No new matter has been added. Support for the claims is found on page 9, line 33 to page 10, line 2 and page 21, line 17.

1. Objections

It is asserted that the application does not contain an abstract of the disclosure. In response, an abstract of the application was filed with PCT/CA00/00042. A replacement copy of the abstract is submitted herewith.

It is asserted that the amendment filed February 26, 2002 does not comply with revised 37 CFR 1.121. In response, Applicants herewith submit amendments to the specification in proper form. These amendments contain SEQ ID NOS. Furthermore, the specification has been amended where needed to refer to Figure 3A, Figures 3B-3F, Figures 19 A-E.

The drawings are objected to because each Figure must be labeled separately using a number and a letter identifier. Additionally, the SEQ ID NOS must be shown in Figures 2, 3B-E, 4, 5 and 7-9. In response, Applicants herewith submit amended Figures 2, 3B-F, 4, 5 and 7-

Applicants also submit herewith a certified copy of the priority application.

2. Claim Rejection – 35 USC 112, Second Paragraph

Claims 29-31 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite. A number of assertions are made and will be addressed in turn.

2.1 Recitation of "derivative"

It is asserted that it is unclear as to what is a "derivative". Applicants respectfully traverse the rejection. However, in order to advance prosecution, this term has been deleted from the claims.

2.2. Recitation of "Ras-binding fragment of GRF4" and "GRF4-binding fragment of Ras."

It is asserted in the Office Action that it is not clear what fragment of GRF4 is the "Ras-binding fragment of GRF4" and what fragment of Ras is the "GRF4-binding fragment of Ras" in claims 29 and 31. Applicants respectfully traverse the rejection. However, in order to advance prosecution, these terms have been deleted from the claims.

2.3 Claim 30

Claim 30 is considered to be indefinite for reciting "Rap1-binding fragment of GRF4" and "GRF4-binding fragment of Rap1." Applicants respectfully traverse the rejection. However, in order to advance prosecution, these terms have been deleted from the claims.

2.4 Claims 29 and 30

Claims 29 and 30 have been rejected as indefinite for not achieving the goal of modulating the activity of an isolated polypeptide as stated in the preamble. As suggested by the Examiner, the claims 29 and 30 have been amended to recite determining whether binding between (i) and (ii) is modulated compared to a control sample in which GRF4 and Ras (or Rap1) are incubated in the absence of compound. Furthermore, claims 29 and 30 as amended recite that an increase or decrease in binding of GRF4 and Ras/Rap1 in the presence of the compound indicates that the compound modulates the interaction of GRF4 and Ras/Rap1.

2.5 Claim 31

Claim 31 has been rejected as indefinite for the use of the term "interfere with binding of (i) with (ii)." The Examiner further asserts that it is not clear how interference can be concluded without reference to a control assay conducted in the absence of compound. Applicants respectfully traverse the rejection. However, in order to advance prosecution, the phrase "interfere with binding of (i) with (ii)" has been deleted from claim 31. Amended claim 31 refers to "inhibition of binding". Further, claim 31 has been amended to recite determining whether binding between (i) and (ii) is inhibited compared to a control sample in which GRF4 and Ras are incubated in the absence of compound, wherein an inhibition of binding in the presence of the compound indicates that the compound reduces cell proliferation.

The Examiner also asserts that it was not clear how the method indicates that cell proliferation reduced since no cell proliferation was measured. The method relates to an assay that identifies compounds that inhibit GRF4 and Ras binding. The Applicants have demonstrated that GRF4 activates Ras. The oncogenic effects of Ras are well known in the art. The Applicants have also shown that GRF4 is oncogenic (see, for example, the transformation assay on page 36 line 29 to page 37, line 21 in which cells transfected with a GRF4 construct grew faster, achieved higher saturation density and induced foci formation. Foci formation, the site where a single transformed cell proliferates and forms a prolific mass of transformed cells, shows a loss of cell-cell contact, a hallmark of cellular transformation). Therefore, inhibiting GRF4 binding to Ras will inhibit cell proliferation.

2.6 Meaning of GRF4

Claims 29-31 were rejected as indefinite because the name GRF4 does not provide any structural or functional limitation on the claim and the metes and bounds of the claim cannot be determined. The Applicants submit that the application discloses a novel function for a class of compounds called GRF4 (see, for example, page 9, lines 27-32). The Ras activating function of these compounds was not known prior to this invention. The Applicants further describe the characteristic recognizable sequence motifs and domains which are identified by amino acid and nucleotide number (Table 1 on page 11) and characterized in detail (page 11, line 32 to page 14, line 16). A schematic

diagram of GRF4 was provided in figure 3a. The Applicants submit that this description allows a skilled person to clearly determine the metes and bounds of the claims. As will be discussed in further detail below, sufficient information is provided about GRF4. It is not necessary to identify by SEQ ID NO.

In view of the above arguments and amendments, Applicants assert that the rejection of the claims under 35 U.S.C. 112, second paragraph have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

3. Claim Rejection – 35 USC 112, First Paragraph-Lack of Enablement

Claims 29-31 have been rejected under 35 USC 112, first paragraph, on the basis that the specification, while being enabling for a method of identifying a compound which modulates the interaction of GRF4 with Ras or the interaction of GRF4 with Rap 1 and a method for evaluation of the cell proliferation reducing properties of a compound that reduces the binding of GRF4 with Ras, does not reasonably provide enablement for the use of derivatives or certain binding fragments. As noted above, amended claims 29-31 do not include "derivatives".

It is asserted that claims 29 and 30 do not disclose what indicates when the binding between (i) and (ii) is modulated. As noted above, the amended claims 29 and 30 recite comparison to a control sample in which GRF4 and Ras (or Rap1) are incubated in the absence of compound and further recite that an increase or decrease in binding of GRF4 and Ras/Rap1 in the presence of the compound indicates that the compound modulates the interaction of GRF4 and Ras/Rap1.

It is asserted that claim 31 lacks enablement for the use of the term "interfere with binding of (i) with (ii)." As noted above, the phrase "interfere with binding of (i) with (ii)." has been deleted from claim 31. Amended claim 31 refers to "inhibition of binding". As further noted above, an enabling disclosure is provided with respect to the relationship of "inhibition of binding" and "reducing cell proliferation". The Applicants have demonstrated that GRF4 activates Ras. The oncogenic effects of Ras are well known in the art. The Applicants have also shown that GRF4 is oncogenic as shown on page 36 line 29 to page 37, line 21 in which cells transfected with a GRF4 construct grew faster, achieved higher saturation density and induced foci formation. Foci formation, the

site where a single transformed cell proliferates and forms a prolific mass of transformed cells, shows a loss of cell-cell contact, a hallmark of cellular transformation. Therefore, inhibiting GRF4 binding to Ras will inhibit cell proliferation.

In view of the above amendments and arguments, Applicants assert that the rejections under 35 U.S.C. 112, first paragraph, lack of enablement have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

4. Claim Rejection – 35 USC 112, First Paragraph-Lack of Adequate Written Description

Claims 29-31 have been rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. It is asserted that an adequate description is not provided for GRF4, Ras and Rap1 or derivatives thereof. In the Examiner's view, only the use of the polypeptide SEQ ID NO:2, 4, Ras and Rap1 in the methods of claims 29-31, but not the full breadth of the claims meets the written description provision of 35 U.S.C. 112, first paragraph.

Applicants respectfully traverse the rejection. However, in order to advance prosecution, "derivatives" of GRF4, Ras and Rap1 have been removed. It is the Applicants' view that an adequate description in the specification is provided in the specification of GRF4 or a portion of GRF4 selected from the group consisting of a Ras association domain or a CDC25-related GEF domain. It is submitted that GRF4 does not require definition by reference to a specific sequence. The claims refer to GRF4, rather than SEQ ID NO:2 because the invention relates to a new class of Ras guanine nucleotide exchange factors. The class of GRF4 polypeptides was completely unknown prior to this invention. The importance of this invention is shown by its publication in the journal Current Biology (Pham N., Cheglakov I., Koch A., de-Hoog C., Moran MF and Rotin D. The guanine nucleotide exchange factor CNrasGEF activates Ras in response to cAMP and cGMP. Curr. Biol. 10:555-558, 2000.).

The Applicants submit that the application includes more written description than was identified by the Examiner. According to the MPEP §2163, the Applicants may disclose any sufficient combination of relevant, identifying characteristics, such as

structure or other physical and/or chemical properties. This section of the MPEP specifically address the types of identifying characteristics that need to be disclosed with respect to biomolecules:

> For some biomolecules, examples of identifying characteristics include a sequence, structure binding affinity, binding specificity, molecular weight, and length. Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. For example, unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities, or antibody cross-reactivity may be sufficient to show possession of the claimed invention to one of skill in the art.

In characterizing this class, the Applicants have described the key structural and functional domains of a GRF4 compound, which include, in amino to carboxyl order, a cyclic nucleotide monophosphate (cAMP/cGMP)-Binding domain (cNMP-BD), a Ras exchange motif (REM), PDZ and Ras association (RA) domains, CDC25-related GEF domain, PY motifs responsible for binding to the Nedd4-WW domain, and a COOH-terminal SaV sequence conforming to PDZ binding motif (described in detail on pages 9, line 33 to page 10, line 2 and page 11, line 21 to page 14, line 16). A schematic diagram of GRF4 was provided in figure 3a. The Applicants provided an exemplary sequence of a GRF4 in figure 3b (SEQ ID NO:2). Other GRF4 sequences were identified, such as the *Drosophila* GRF4 sequence, shown in part in figure 4a. The Applicants also provided direction on how to identify other GRF4's (page 17, line 1 to page 18, line 10 and page 20, lines 18-25) and a test for GRF4 activity (page 18, lines 11-16).

In conclusion, the Applicants submit that the disclosure in the application reasonably conveys to the artisan that the Applicants have possession of the claimed subject matter, which is methods using the class of GRF4 compounds, rather than just SEQ ID NO:2. Therefore, Applicants respectfully request that the rejection of the claims under 35 U.S.C. 112, first paragraph as lacking written description be withdrawn.

Conclusion

In view of the above arguments, Applicant asserts that the rejections have been overcome. Therefore, Applicant respectfully requests that the rejections be withdrawn and submit that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment of application.

Respectfully submitted,

Date: 11/10/03

Cheryl H. Agris, Ph.D.
Reg. No. 34,086
Attorney at Law
P.O. Box 806
Pelham, N.Y. 10803
(914) 712-0093